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Fosfomycin for Non-Urinary Tract Infections: a systematic review

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SUMMARY

Introduction: Although fosfomycin is currently approved for treating urinary tract infections, it is increasingly being used as salvage therapy for various infectious syndromes outside the urinary tract. This systematic review evaluates clinical and microbiological cure rates in patients with bacterial infections not restricted to the urinary tract where fosfomycin was used off-label.
Materials and Methods: Articles from two databases (Pubmed and Scopus) were reviewed. The dosage, route, and duration of fosfomycin therapy along with the details of adjunctive antimicrobial agents were noted. The final outcomes captured were clinical or microbiological cures.
Results: A total of 649 articles, not including duplicates, were selected for the title and abstract screening. After title and abstract screening, 102 articles were kept for full-text screening. Of the 102 articles, 23 studies (n=1227 patients) were kept in the final analysis. Of the 1227 patients, 301 (25%) received fosfomycin as monotherapy, and the remaining 926 (75%) received fosfomycin in combination with at least one other antimicrobial agent. Most of the patients received intravenous fosfomycin (n=1046, 85%). *Staphylococcus* spp and Enterobacteriaceae were the most common organisms. The pooled clinical and microbiological cure rates were 75% and 84%, respectively.
Conclusion: Fosfomycin has moderate clinical success in patients with non-urinary tract infections, especially when used with other antimicrobials. Due to the paucity of randomized controlled trials, fosfomycin's use should be limited to situations where no alternatives are supported by better clinical evidence.

Keywords: bacteraemia, Central Nervous System, fosfomycin.

INTRODUCTION

Fosfomycin is a phosphonic antibiotic first discovered in Spain in the late 1960s from cultures of *Streptomyces fradiae* [1]. Its mechanism of action involves the inhibition of peptidoglycan synthesis associated with the MurA gene [1]. Fosfomycin is a broad-spectrum antimicrobial covering Gram-negative (Enterobacteriaceae, *Pseudomonas* spp.) and Gram-positive (*Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus* spp.) organisms [1]. It has no known cross-resistance or cross-allergy to other antibiotic classes [1]. Although oral fosfomycin has been approved for treating urinary tract infections, fosfomycin is increasingly being used off-label (drug repurposing) for other infec-

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tious syndromes [1]. Considering increasing antimicrobial resistance coupled with a relative absence of new antimicrobial development, there is a need to evaluate available drugs, such as fosfomycin, for non-approved indications. This review aims to study the effect of intravenous or oral fosfomycin on clinical and microbiological cures in patients with systemic bacterial infections other than those restricted to the urinary tract.

MATERIALS AND METHODS

The systematic review was done following PRISMA standards. The following search string was used in two databases (Pubmed and Scopus): [(fosfomycin) AND (oral OR intravenous OR iv) AND (bone OR osteo OR joint OR articular OR arthritis OR osteoarticular OR spondylitis OR discitis OR spondylodiscitis OR blood OR bacteraemia OR septicaemia OR sepsis OR meningitis OR nervous OR CNS OR neurological OR brain) AND (clinical OR microbiological OR culture) AND (human OR patient)]. The Scopus search string was limited to title, abstract and keywords. All articles between the beginning of 1975 and the end of January 2023 were included for title-abstract screening. Two independent reviewers (SC and SDA) did the title and abstract screening, and a third reviewer (NG) was consulted when there was a disagreement. Those full texts of the article included after the title-abstract screening were screened for the eligibility criteria. After the full-text screening, article data was entered into a Microsoft Excel workbook.

Those studies that had patients with bone/joint infection (BJI), bacteraemia/septicaemia (secondary to any site including urinary tract), involvement of the central nervous system (CNS) or other organ systems with positive aerobic bacterial culture treated with oral or intravenous fosfomycin were included. All study types were eligible, including randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and case series. Descriptive observational studies with a single arm were considered as case series. Analytical observational studies with follow-up and the presence of a comparator arm were considered as cohort studies. Those studies where exposure to fosfomycin was assigned randomly were considered as randomised controlled trials. Case reports and those patients with non-bacteremic urinary tract infections were excluded. *In-vitro* studies, animal studies, pharmacological modelling studies and studies where fosfomycin was used as prophylaxis were excluded. Wherever possible, an attempt to translate the non English-articles was made to extract the data.

The clinical details of all patients where fosfomycin was used as monotherapy or combination were recorded. The dosage, route, and duration of fosfomycin therapy were noted. The details of infectious syndromes, identified organisms of interest (Enterobacteriaceae, *Staphylococcus aureus*, *Staphylococcus epidermidis, Enterococcus spp and Pseudomonas aeruginosa)* and details of combination therapy were also recorded. Those studies which had patients with both urinary and non-urinary infections, only those data that were exclusively available for non-urinary infections were extracted in this review. The final outcomes in the form of clinical or microbiological cures were recorded. The mortality rate in each study was also reviewed. This systematic review was reported according to the PRISMA 2020 checklist.

RESULTS

A total of 749 articles (166 for Pubmed, 583 from Scopus) were selected for the title and abstract screening. A total of 649 articles were selected after 100 duplicates were deleted. After title and abstract screening, 102 articles were kept for full-text screening. Of the 102 articles, 23 studies were kept in the final analysis (Figure 1) [2-24].

A total of 1227 patients were included from 23 studies (1977 to 2023) in the final analysis. Most studies were single-arm case series (Table 1). There were three RCTs included in this SR. Most studies were reported in Europe (Table 1).

A total of 516 (42%) patients were treated for bacteraemia/septicaemia (Table 2). A total of 20% (n=243) of patients had bone and joint infections (Table 2). Of these, the majority were native bone and joint infections (n=243, 20%). The lower respiratory tract (LRT), central nervous system (CNS), intra-abdominal/gastrointestinal tract and skin/soft tissue were involved in 11% (n=139), 6% (n=77), 7% (n=87) and 2% (n=27) patients, respectively (Table 2).

All the included patients in this SR had a confirmed bacteriological diagnosis. In some studies, however, details of organisms causing non-urinary tract infections were not available separately.

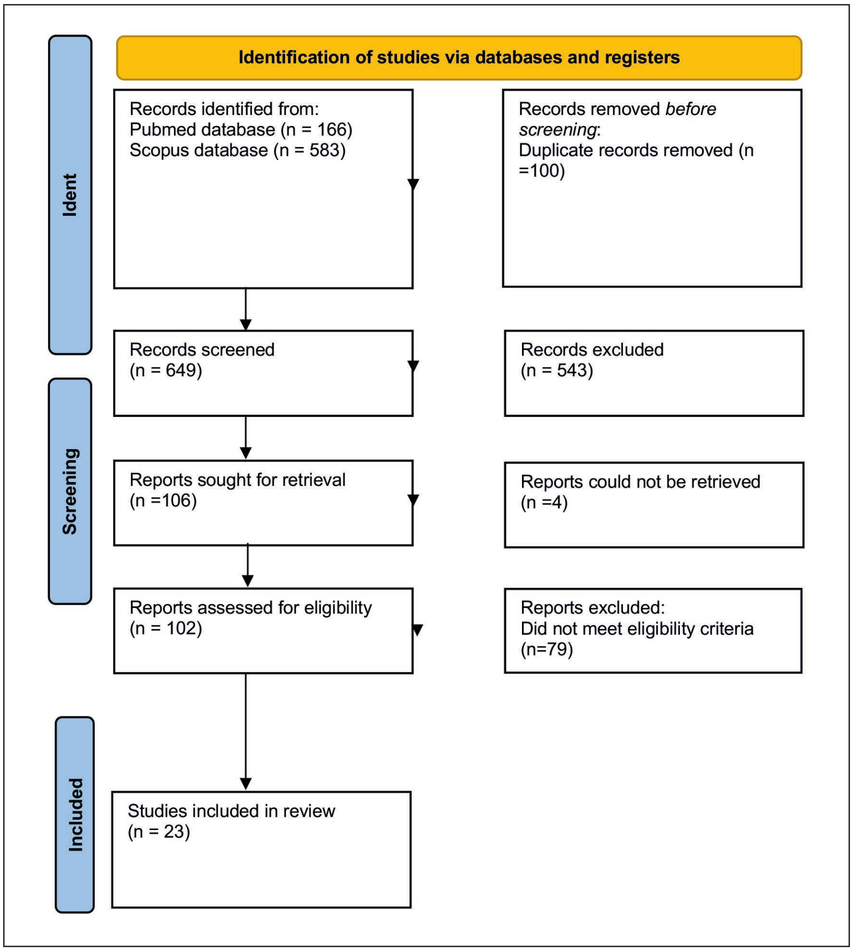

Figure 1 - Prisma chart showing the screening and inclusion process of fosfomycin-related articles.

Table 1 - Details of the studies where fosfomycin was used for the treatment of infections outside the urinary tract.

Sn	*Author/Year*	*Study Design*	*Country*	*Total number*
1	Tseng 2023 [20]	Cohort study	Taiwan	48
2	Aysert-Yildiz 2022 [21]	Case series	Turkey	68
3	Sojo-Dorado 2022 [22]	Randomised Clinical Trial	Spain	70
4	Ballouz 2021 [23]	Analytical cross-sectional study	Lebanon	26
5	Gatti 2022 [24]	Case series	Italy	6
6	Frieler 2021 [2]	Case series	USA	14
7	Putensen 2019 [3]	Case series	Germany, Austria	209
8	Florent 2011 [4]	Case series	France	72
9	C-A 2010 [5]	Case series	Spain	7
10	C-A 2009 [6]	Case series	Spain	6
11	Fitoussi 2007 [7]	Case series	France	18
12	Corti 2003 [8]	Cohort study	Switzerland	70

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Sn	*Author/Year*	*Study Design*	*Country*	*Total number*
13	Hasegawa 1998 [9]	Randomised clinical trial	Japan	145
14	Meissner 1989 [10]	Case series	Germany	60
15	Baron 1986 [11]	Cohort study	France	17
16	Pujol 2021 [12]	Randomised Clinical Trial	Spain	74
17	Del Río 2014 [13]	Case series	Spain	16
18	Nakamura 1985 [14]	Case series	Japan	6
19	Portier 1985 [15]	Case series	France	23
20	Dai 1981 [16]	Case series	China	184
21	Sicilia 1977 [17]	Case series	Spain	12
22	Baquero 1977 [18]	Case series	Spain	26
23	Figueroa 1977 [19]	Cohort study	Spain	50

Abbreviations: Sn-Serial number, USA- United States of America.

Table 2 - Details of the syndromes for which fosfomycin was prescribed as treatment.

Sn	*Author*	*N*	*Bacteraemia/ septicaemia*	*Bone/joint infection*	*CNS infection*	*LRTI*	*Skin Soft tissue infection*	*Intraabdominal/ GI*
1	Tseng 2023 [20]	48	48 (100%)					
2	Aysert-Yildiz 2022 [21]	68	19 (20%)	2 (2%)		28 (30%)	9 (10%)	10 (11%)
3	Sojo-Dorado 2022 [22]	70	70 (100%)					
4	Ballouz 2021 [23]	26	23 (88%)			3 (12%)		
5	Gatti 2022 [24]	6	3 (50%)			3 (50%)		
6	Frieler 2021 [2]	14		14 (100%)				
7	Putensen 2019 [3]	209	49 (23%)	23 (11%)	45 (21%)	32 (15%)	14 (7%)	23 (11%)
8	Florent 2011 [4]	72	5 (7%)	33 (46%)	11 (15%)	1 (1%)	4 (5%)	
9	C-A 2010 [5]	7		7 (100%)				
10	C-A 2009 [6]	6		6 (100%)				
11	Fitoussi 2007 [7]	18		18 (100%)				
12	Corti 2003 [8]	70		70 (100%)				
13	Hasegawa 1998 [9]	145	109 (75%)			19 (13%)		
14	Meissner 1989 [10]	60		60 (100%)				
15	Baron 1986 [11]	17	15 (88%)					
16	Pujol 2021 [12]	74	74 (100%)					
17	Del Río 2014 [13]	16	16 (100%)					
18	Nakamura 1985 [14]	6						6 (100%)
19	Portier 1985 [15]	23	3 (13%)	10 (43%)	9 (39%)			
20	Dai 1981 [16]	184	6 (3%)			53 (29%)		48 (26%)
21	Sicilia 1977 [17]	12			12 (100%)			
22	Baquero 1977 [18]	26	26 (100%)					
23	Figueroa 1977 [19]	50	50 (100%)					

Abbreviations: N-Total number of patients, CNS-Central Nervous System, LRTI- Lower Respiratory Tract Infection, GI- Gastrointestinal.

A total of 787 patients had a confirmed bacterial diagnosis of interest. The following pathogens were isolated as responsible for the infection: *Staphylococcus* spp. (n=341, 44%), *Enterobacteriaceae* (n=335, 43%), *Enterococcus* spp. (n=79 or 10%%) and *Pseudomonas* spp. (n=32 or 4%) (Table 3). The single most common pathogen was *Staphylococcus aureus* (n=265 or 34%).

Of the 1227 patients, 24% (n = 301) received fosfomycin as monotherapy, and 76% (n=926) received fosfomycin in combination with at least one other antimicrobial agent. Most patients received fosfomycin (n = 1046, 85%) as injectable fosfomycin therapy (Table 4). The average dose of fosfomycin in different studies ranged from 3 to 24 grams daily.

Table 3 - Details of the microbial aetiology involving various systems for which fosfomycin was prescribed.

Sn	*Author*	*Enterobacteriaceae*	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*Enterococcus spp*	*Pseudomonas spp*
1	Tseng 2023 [20]				48 (100%)	
2	Aysert-Yildiz 2022 [21]	68 (100%)				
3	Sojo-Dorado J 2022 [22]	70 (100%)				
4	Gatti 2022 [24]					6 (100%)
5	Frieler 2021 [2]		2 (14%)	10 (71%)	2 (14%)	1 (7%)
6	Putensen 2019 [3]	79 (38%)	58 (28%)	37 (18%)	28 (13%)	
7	Florent 2011 [4]	24 (33%)	12 (17%)			13 (18%)
8	C-A 2010 [5]	1 (14%)	5 (71%)			
9	C-A 2009 [6]	1 (17%)	5 (83%)			
10	Fitoussi 2007 [7]		8 (44%)			
11	Corti 2003 [8]		15 (21%)	6 (9%)		
12	Hasegawa 1998 [9]	4 (3%)	1 (1%)	3 (2%)	1 (1%)	
13	Meissner 1989 [10]	7 (12%)	34 (57%)	15 (25%)		12 (20%)
14	Baron 1986 [11]		17 (100%)			
15	Pujol 2021 [12]		74 (100%)			
16	Del Río 2014 [13]		16 (100%)			
17	Nakamura 1985 [14]	5 (83%)				
18	Portier 1985 [15]		18 (78%)	5 (22%)		
19	Bacquer 1977 [18]	26 (100%)				
20	Figueroa 1977 [19]	50 (100%)				

Table 4 - Details of route, dose and duration of fosfomycin therapy.

Sn	*Author/Year*	*N*	*Monotherapy#*	*Injectable##*	*Daily dose*	*Duration of therapy (days)*
1	Tseng 2023 [20]	48	0	48 (100%)	12 g	7.5 (3-14)
2	Aysert-Yildiz 2022 [21]	68	1 (1%)	68 (100%)	12 (8-16)	12 (8-14)
3	Sojo-Dorado 2022 [22]	70	70 (100%)	70 (100%)	16 g	5.4±0.9
4	Ballouz 2021 [23]	26	0	26 (100%)	12-16 g	6-11.5
5	Gatti 2022 [24]	6	0	6 (100%)	16 g	
6	Frieler 2021 [2]	14	0	14 (100%)	15 g	84 (at-least)
7	Putensen 2019 [3]	209	2 (1%)	209 (100%)	13.7±3.5 g/d	12.4±8.6

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Sn	Author/Year	N	Monotherapy#	Injectable##	Daily dose	Duration of therapy (days)
8	Florent 2011 [4]	72	0	72 (100%)	12 g	11
9	C-A 2010 [5]	7	0	0	3 g	180
10	C-A 2009 [6]	6	0	0	3 g	180
11	Fitoussi 2007 [7]	18	0	18 (100%)		7
12	Corti 2003 [8]	70	23 (33%)	70 (100%)	200 mg/kg	17.5 to 21.7
13	Hasegawa 1998 [9]	145	0	145 (100%)	4 g	8
14	Meissner 1989 [10]	60	60 (100%)	60 (100%)	15 g	13.9
15	Baron 1986 [11]	17	0	17 (100%)	237 mg/kg/day	17
16	Pujol 2021 [12]	74	0	74 (100%)	8 g	14
17	Del Río 2014 [13]	16	0	16 (100%)	8 g	28
18	Nakamura 1985 [14]	6	6 (100%)	6 (100%)	4 g	5-10
19	Portier 1985 [15]	23	0	23 (100%)	150-200 mg/kg	16.5-17.6
20	Dai 1981 [16]	184	118 (64%)	66 (36%)	oral-2-4 g, iv-5-16 g	7-21
21	Sicilia 1977 [17]	12	0	12 (100%)	24 g	5-17
22	Baquero 1977 [18]	26	6 (23%)	26 (100%)	300-500 mg/kg/day	14-28
23	Figueroa 1977 [19]	50	15 (30%)	–	2-10 g	15-20

Notes: Sn- Serial number, mg- milligrams, g- grams, kg- kilograms.
Percentage in bracket indicates the number of patients who were given monotherapy in the study. The rest of the patients in that study were given combination therapy.
Percentage in bracket indicates the number of patients who were given intravenous fosfomycin in the study. The rest of the patients in that study were given oral Fosfomycin.

The most common duration of treatment in various studies ranged from 1 to 12 weeks (Table 4).
Of the 926 patients who received combination therapy, the most commonly used adjunctive antibiotics were cephalosporins, daptomycin, carbapenems, penicillin formulations, glycopeptides, aminoglycosides, beta-lactam & beta-lactamase inhibitor combination, fluoroquinolones, metronidazole, chloramphenicol, linezolid, macrolides and rifampicin (Table 5).
The clinical cure ranged from 52% to 100%, while the microbiological cure ranged from 70% to 100% (Table 6). The pooled clinical and microbiological cure rates were 75% (860/1146) and 84% (270/322), respectively. A total of 95 deaths were reported, and the percentage of mortality in studies ranged from 3-48% (Table 6).

Table 5 - Details of adjunctive antibiotics (used for a cumulative of 10 cases) used with fosfomycin.

Sn	Author	Pn	BL/BLI	Ceph	Carb	Rif	AG	Glyc	Dapt	Lz	FQ	Chlor	Macro	Metro
1	Tseng 2023 [20]								48 (21%)					
2	Frieler 2021 [2]			1 (7%)			3 (21%)	11 (79%)	11 (79%)					
3	Putensen 2019 [3]	22 (10%)	30 (14%)	58 (28%)	102 (49%)	7 (3%)	13 (6%)	66 (32%)	10 (5%)	13 (6%)	23 (11%)		12 (6%)	26 (12%)
4	C-A 2010 [5]					3 (43%)		1 (14%)		1 (14%)	3 (43%)			
5	C-A 2009 [6]					1 (17%)				1 (17%)				

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Sn	*Author*	*Pn*	*BL/BLI*	*Ceph*	*Carb*	*Rif*	*AG*	*Glyc*	*Dapt*	*Lz*	*FQ*	*Chlor*	*Macro*	*Metro*
6	Fitoussi 2007 [7]			18 (100%)										
7	Corti 2003 [8]	40 (57%)	4 (6%)				1 (1%)							
8	Hasegawa 1998 [9]			145 (100%)										
9	Pujol 2021 [12]								74 (100%)					
10	Del Río 2014 [13]				16 (100%)									
11	Portier 1985 [15]			23 (100%)										
12	Sicilia 1977 [17]	7 (58%)					5 (42%)							
13	Bacquero 1977 [18]	2 (7%)					18 (69%)							
14	Figueroa 1977 [19]	13 (26%)										22 (44%)		

Notes: Pn = penicillin formulations, BL/BLI = beta-lactam & beta-lactamase inhibitor combination, Ceph = cephalosporins, Carb = carbapenems, Rif = rifampicin, AG = aminoglycosides, Glyc = glycopeptides, Dapt = daptomycin, Lz = linezolid, Fq = fluoroquinolones, Chlor = chloramphenicol, Macro = macrolides, Metro = metronidazole.

Table 6 - Summary of the predominant syndrome, predominant organism and the predominant adjunctive antibiotic used in each study, along with the outcomes of a study.

Sn	*Author*	*N*	*Monotherapy or combination*	*Predominant syndrome#*	*Predominant organism#*	*Predominant adjunctive antibiotic#*	*Clinical Cure*	*Micro cure*	*Death*
1	Tseng 2023 [20]	48	Combination	Bacteraemia	Enterococcus	Dapt			23 (48%)
2	Aysert-Yildiz 2022[21]	67	Mono or Combination	LRTI	Enterobac	Mero and Poly	46 (69%)		27 (40%)
3	Sojo-Dorado 2022 [22]	70	Mono	Bacteraemia	Enterobac	–	59/61 (97%)	48/58 (83%)	2 (3%)
4	Ballouz 2021 [23]	26	Combination	Bacteraemia	Enterobac	Tige	18 (69%)	8/8 (100%)	
5	Gatti 2022 [24]	6	Combination	Bacteraemia	Pseudomonas	Cefiderocol		5 (83%)	1 (17%)
6	Frieler 2021 [2]	14	Combination	BJI	Staph	Glycop and dapt	–	–	0
7	Putensen 2019 [3]	209	Mono or Combination	Bacteraemia & CNS	Staph and Enterobac	Carba	148 (81%)	63 (70%)	15 (7%)
8	Florent 2011 [4]	72	Combination	BJI	Enterobac	–	62 (86%)	–	–
9	C-A 2010 [5]	7	Combination	BJI	Staph	Rif and FQ	7 (100%)	–	0
10	C-A 2009 [6]	6	Combination	BJI	Staph	Rif and Lz	5 (83%)	5 (83%)	0

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Sn	Author	N	Monotherapy or combination	Predominant syndrome#	Predominant organism#	Predominant adjunctive antibiotic#	Clinical Cure	Micro cure	Death
11	Fitoussi 2007 [7]	18	Combination	BJI	Staph	Ceph	15 (83%)	–	0
12	Corti 2003 [8]	70	Mono or Combination	BJI	Staph	Pn	70 (100%)	–	0
13	Hasegawa 1998 [9]	145	Combination	Bacteraemia	Enterobac	Ceph	75 (52%)	–	0
14	Meissner 1989 [10]	60	Monotherapy	BJI	Staph	–	39 (65%)	–	0
15	Baron 1986 [11]	17	Combination	Bacteraemia	Staph	–	16 (94%)	16 (94%)	1 (6%)
16	Pujol 2021 [12]	74	Combination	Bacteraemia	Staph	Dapt	40 (54%)	74 (100%)	18 (24%)
17	Del Río 2014 [13]	16	Combination	Bacteraemia	Staph	Carba	11 (69%)	16 (100%)	5 (31%)
18	Nakamura 1985 [14]	6	Monotherapy	GI	Enterobac	–	6 (100%)	–	0
19	Portier 1985 [15]	23	Combination	BJI & CNS	Staph	Ceph	21 (91%)	–	1 (4%)
20	Dai 1981 [16]	184	Mono or Combination	LRTI & GI	–	–	151 (82%)	–	
21	Sicilia 1977 [17]	12	Combination	CNS	–	Pn and AG	10 (83%)	–	2 (17%)
22	Baquero 1977 [18]	26	Mono or Combination	Bacteraemia	Enterobac	AG	21 (81%)	–	–
23	Figueroa 1977 [19]	50	Mono or Combination	Bacteraemia	Enterobac	Pn and Chlor	40 (80%)	40 (80%)	–

The details of syndromes, organisms, and antibiotics are available in the previous tables.
Abbreviations: Sn: Serial number, Micro: Microbiological, CNS: Central Nervous System, BJI: Bone Joint infection, GI: Gastrointestinal, LRTI: Lower Respiratory Tract Infection, Staph: Staphylococcus, Enterobac: Enterobacteriaceae, Glycop: Glycopeptide, Dapt: Daptomycin, Carba: Carbapenem, Rif: Rifampicin, FQ: Fluoroquinolone, Lz: Linezolid, Ceph:Cephalosporin, Pn: Penicillin, AG: Aminoglycoside, Chlor: Chloramphenicol.

DISCUSSION

Fosfomycin's relatively low molecular weight facilitates penetration throughout body tissues and, therefore, is potentially useful in treating a wide variety of syndromic infections [1]. Its clinical efficacy has been demonstrated for uncomplicated urinary tract infections, and it remains recommended as the first-line drug for this syndrome in many guidelines [1]. However, increasing evidence suggests it works well for complicated urinary tract infections as well [25]. In a randomized controlled trial (RCT) involving 465 patients with complicated urinary tract infections, fosfomycin was found to have a better overall clinical success when compared to piperacillin-tazobactam [25]. Since the efficacy of fosfomycin has been well established for non-bacteremic urinary tract infections, this review focused on non-urinary tract infections primarily.

Older systematic reviews focusing on a particular syndrome or formulation exist. Therefore, we broadened our inclusion criteria to include syndromes such as lower respiratory tract infection, intra-abdominal infection, skin-soft tissue infection and bacteraemia [26, 27]. Considering the increasing prevalence of resistant Gram-negative organisms in BJI and the requirement for long-duration therapy, fosfomycin has been viewed as an attractive option. It is interesting to note that the fosfomycin concentration in the bone has been shown to be higher than the minimum inhibitory concentrations of most responsible pathogens [10]. Fosfomycin was found to be useful in BJI with clinical and microbiological cures of 65-100% and 83%, respectively (Table 4). It was also found to be useful in patients with bacteraemia with clinical and microbiological success in 54-94% to 80-100%, respectively, in this review (Table 4). Studies with smaller sample sizes showed utility in CNS and intra-abdominal infections as well.

Most studies in our review used fosfomycin in combination therapy. There were only three studies where all patients were treated with fosfomycin monotherapy [10, 14, 22]. The proportion of clinical cures in these three studies was 65%, 100%, and 97% respectively [10, 14, 22]. In the studies that used fosfomycin only as a combination therapy, the clinical cure rates varied between 52-100%. In a study where both monotherapy and combination therapy was given, there was no difference between the outcomes in patients with osteomyelitis who were given monotherapy or combination therapy [8]. In another study on the use of fosfomycin for typhoid fever, combination therapy fared better than monotherapy [19]. The combination therapy in *Staphylococcus* spp. included a range of antibiotics such as cephalosporins, carbapenems, glycopeptides, daptomycin, rifampicin, linezolid and fluoroquinolones. Combination therapy in Enterobacteriaceae included penicillin, cephalosporins, aminoglycoside, and carbapenems.

The most common organisms for which fosfomycin was prescribed were *Staphylococcus* spp. and Enterobacteriaceae. In Gram-positive organisms, *Staphylococcus* spp. is known to be commonly susceptible to fosfomycin. Some reports of acquired resistance in *Staphylococcus epidermidis* have been noted but similar resistance has not been seen in *Staphylococcus aureus.* Our study did not differentiate between *S. aureus* and *S. epidermidis,* as outcomes were rarely described according to the species in the reviewed studies. Fosfomycin has been shown to act synergistically with cefazolin, flucloxacillin, vancomycin and daptomycin in *Staphylococcus* spp. [28]. Fosfomycin and daptomycin are synergistic against vancomycin-resistant Enterococcus [29]. Due to the intracellular activity of fosfomycin against *Staphylococcus* spp., the medication has also demonstrated activity against biofilms, especially when combined with rifampicin [30, 31]. Studies that predominantly included *Staphylococcus* spp. in our review had variable clinical and microbiological cure rates. Most observation studies in the review showed good clinical success with fosfomycin on *Staphylococcus* spp. but one of the included RCTs showed no significant difference with the addition of fosfomycin to daptomycin in patients with MRSA [12]. However, it must be noted that fosfomycin was used at a low dose here (8 grams per day), and there were fewer microbiological failures with combination therapy. On subgroup analysis, the combination was better for patients under 73 years of age and those with more severe infections. In a study on patients with *S. aureus* bacteraemia, no difference was found between monotherapy vs combination therapy (some of which included fosfomycin) in terms of 90-day mortality [32]. However, combination therapy was better than monotherapy when 180-day mortality was considered as the outcome [32]. This study was not included in our review as fosfomycin-specific outcomes were unavailable separately.

In our review, clinical cure rates in studies that included Enterobacteriaceae varied substantially. Due to its unique mechanism of action, fosfomycin maintains activity against beta-lactamase-producing Enterobacteriaceae [33, 34]. The activity of fosfomycin against resistance mechanisms such as KPC seems to be enhanced with combination drugs such as ceftazidime-avibactam [35]. Some studies have shown that fosfomycin use is associated with variable success in *Pseudomonas* spp. and *Acinetobacter* spp.

This systematic review has several limitations. Due to the absence of quality randomized controlled trials, fosfomycin was not compared with comparator drugs, making it difficult to conclude on the drug's efficacy. Also, the data was taken from studies where the primary objective was not to evaluate fosfomycin. In studies where fosfomycin was used as combination therapy, it was difficult to assess whether or not the addition of fosfomycin significantly impacted outcomes. The studies had considerable heterogeneity, especially in how outcomes were defined. The data on antimicrobial susceptibility results were largely absent, and many studies were limited by small sample sizes. The quantitative analysis could not be done due to significant heterogeneity and a lack of comparators. Lastly, there is a possibility that the results are affected by publication bias, as researchers tend not to publish studies with negative results.

In conclusion, fosfomycin has moderate clinical success in patients with non-urinary tract infections caused by *Staphylococcus* spp. and Enterobacteriaceae, especially when used with other antimicrobials. Systematic treatment and outcome data collection should be prioritized to generate real-world evidence supporting or refuting fosfomycin's comparative effectiveness for treating infections beyond the urinary tract. Due to the current paucity of large randomized controlled trials, fosfomycin use outside its present indication should be limited to settings where no evidence-based alternatives exist.

Conflict of interest

Nothing to declare.

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